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L5: Entry 1 of 1 File: USPT Jan 28, 2003

DOCUMENT-IDENTIFIER: US 6511649 B1
TITLE: Vitronectin receptor antagonist pharmaceuticals

Brief Summary Text (106):
[60] In another preferred embodiment, the present invention provides a kit according to Embodiment 58, wherein the chemotherapeutic agent is selected from the group consisting of mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, and leutinizing hormone releasing factor.

CLAIMS:

14. A kit according to claim 12, wherein the chemotherapeutic agent is selected from the group consisting of mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, and leutinizing hormone releasing factor.

L19 ANSWER 8 OF 13 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 94:663775 SCISEARCH
THE GENUINE ARTICLE: PL404
TITLE: INTERACTION OF **LIPOSOME**-ASSOCIATED ALL-TRANS-**RETINOIC ACID** WITH SQUAMOUS CARCINOMA-CELLS
AUTHOR: PARTHASARATHY R; SACKS P G; HARRIS D; BROCK H; MEHTA K (Reprint)
CORPORATE SOURCE: UNIV TEXAS, MD ANDERSON CANCER CTR, DEPT CLIN INVEST, BOX 60, 1515 HOLCOMBE BLVD, HOUSTON, TX, 77030 (Reprint); UNIV TEXAS, MD ANDERSON CANCER CTR, DEPT CLIN INVEST, HOUSTON, TX, 77030; MEM SLOAN KETTERING CANC CTR, DEPT HEAD & NECK, NEW YORK, NY, 00000
COUNTRY OF AUTHOR: USA
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (**SEP 1994**)
Vol. 34, No. 6, pp. 527-534.
ISSN: 0344-5704.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: 26

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Because of their antiproliferative and differentiation-inducing properties, retinoids have been used clinically as therapeutic and chemopreventive agents against squamous-cell carcinomas (SCC). As is the case for many therapeutic agents, however, the administration of retinoids is associated with toxic effects. Because encapsulation of certain drugs in lipid vesicles (liposomes) has been shown to result in reduced toxic effects, we studied the in vitro interaction of **liposome**-encapsulated all-trans-**retinoic acid** (L-ATRA) with a SCC line (MDA 886Ln) and its multicellular tumor spheroid (MTS) model. Various L-ATRA formulations were tested for incorporation of retinoic acid, toxic effects against human red blood cells, uptake and retention by tumor cells, and antiproliferative effects against SCC. Of the different formulations tested, L-ATRA containing diphosphatidyl palmitoylcholine (DPPC) and stearylamine (SA; 9:1, w/w) showed optimal drug incorporation, high stability, and minimal toxicity toward red blood cells and was highly efficacious in delivering ATRA and, thus, in inhibiting the growth of MDA 886Ln and its MTS model. DPPC: SA L-ATRA inhibited the expression of the enzyme keratinocyte transglutaminase in epidermal cells as effectively as did the free drug. These results suggest that liposomes can serve as an effective carrier system for the delivery of retinoids to SCC.

L19 ANSWER 5 OF 13 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1999:64387 SCISEARCH
THE GENUINE ARTICLE: 155LZ
TITLE: Altered metabolism of all-trans-**retinoic acid** in **liposome**-encapsulated form
AUTHOR: Parthasarathy R; Mehta K (Reprint)
CORPORATE SOURCE: UNIV TEXAS, MD ANDERSON CANC CTR, DEPT BIOIMMUNOTHERAPY, BOX 60, 1515 HOLCOMBE BLVD, HOUSTON, TX 77030 (Reprint); UNIV TEXAS, MD ANDERSON CANC CTR, DEPT BIOIMMUNOTHERAPY, HOUSTON, TX 77030
COUNTRY OF AUTHOR: USA
SOURCE: CANCER LETTERS, (**25 DEC 1998**) Vol. 134, No. 2, pp. 121-128.
Publisher: ELSEVIER SCI IRELAND LTD, CUSTOMER RELATIONS MANAGER, BAY 15, SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND.
ISSN: 0304-3835.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 37

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Treatment with all-trans-retinoic acid (ATRA) induces complete remission in many acute promyelocytic leukemia patients. However, plasma drug levels progressively decrease following prolonged treatment with oral ATRA. This decrease is due, at least in pan, to the induced cytochrome P-450-dependent metabolism of ATRA. To investigate if incorporation of **ATRA** in **liposomes** could alter its metabolism, we compared the cellular metabolism of **liposomal-ATRA** (L-**ATRA**) with free drug. Microsomes isolated from the rat liver metabolized L-ATRA to a significantly lower extent than they did free-ATRA. Similarly, in F9 cells, L-ATRA was metabolized at a slower rate than the free drug. These results suggest that L-ATRA may have important clinical implications in terms of slowing down the rate of ATRA metabolism and producing long-term remission in APL patients.

L19 ANSWER 3 OF 13 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1999:567864 SCISEARCH
THE GENUINE ARTICLE: 217TH
TITLE: Assessment of all-trans retinoic acid (ATRA) efficacy as a single agent in primary lymphoid neoplasia
AUTHOR: Swaminathan N; LopezBerestein G; Rudikoff S (Reprint)
CORPORATE SOURCE: NCI, CELLULAR & MOL BIOL LAB, NIH, BLDG 37, ROOM ID08, BETHESDA, MD 20892 (Reprint); NCI, CELLULAR & MOL BIOL LAB, NIH, BETHESDA, MD 20892; UNIV TEXAS, MD ANDERSON CANC CTR, DIV MED, HOUSTON, TX 77030
COUNTRY OF AUTHOR: USA
SOURCE: MEDICAL ONCOLOGY, (**JUL 1999**) Vol. 16, No. 2, pp. 119-128.
Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND.
ISSN: 0736-0118.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: English
REFERENCE COUNT: 50

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB All-trans retinoic acid (ATRA) is currently widely used in the therapy of acute promyelocytic leukemia and is being tested in vitro and in vivo on several other malignancies. Previously ATRA has been shown to inhibit the growth in vitro, of established human myeloma cell lines as well as cultured primary myeloma cells from patients. ATRA acts by down-regulating IL-6-receptor-alpha or gp130 on the surface of the myeloma cells. However, despite its in vitro effects on myeloma cells, ATRA therapy on advanced stage multiple myeloma (MM) patients has so far largely been ineffective. In current studies, we have assessed the efficacy of ATRA therapy against primary murine plasma cell tumors, which are an animal model for human MM, These tumors are induced at about 50% incidence in pristane-primed BALB/c mice by injection of v-raf/v-myc- containing retroviruses and are IL-6 dependent. Using this animal model, we assessed the effect of ATRA as a therapeutic agent against primary tumors at two early time points in disease development. **ATRA** was administered in **liposomal** vesicles (ATRAGEN(R)), since **liposomal-ATRA** has been shown to circumvent clearance mechanisms by hepatic microsomes, which normally occur with free ATRA. In addition, ATRAGEN(R) was previously shown to be less toxic in mice than free ATRA, ATRAGEN(R) was administered beginning on day 25 or day 45 after virus injection and continued twice weekly for 8-11 weeks. ATRAGEN(R) administration begun at either time point did not alter the incidence or the latency of plasma cell tumors compared with control animals. These results suggest that ATRA may not be an effective sole therapy against early MM.

L19 ANSWER 2 OF 13 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1999:164280 SCISEARCH
THE GENUINE ARTICLE: 168GU
TITLE: Aerosol delivery of **liposomal** all-trans-**retinoic acid** to the lungs
AUTHOR: Parthasarathy R; Gilbert B; Mehta K (Reprint)
CORPORATE SOURCE: UNIV TEXAS, MD ANDERSON CANC CTR, DEPT BIOIMMUNOTHERAPY, BOX 60, 1515 HOLCOMBE BLVD, HOUSTON, TX 77030 (Reprint); UNIV TEXAS, MD ANDERSON CANC CTR, DEPT BIOIMMUNOTHERAPY, HOUSTON, TX 77030; UNIV TEXAS, MD ANDERSON CANC CTR, DEPT ENDOCRINOL, HOUSTON, TX 77030; BAYLOR COLL MED, HOUSTON, TX 77025
COUNTRY OF AUTHOR: USA
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (**APR 1999**)
Vol. 43, No. 4, pp. 277-283.
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.
ISSN: 0344-5704.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 33

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose: To optimize the delivery of all-transretinoic acid (ATRA) to lung tissue, we determined the potential of vehiculating the drug in **liposomes** (L-**ATRA**) and delivering it via aerosol.
Liposomes may provide a means to prevent local irritation of lung tissue and reduce pulmonary toxicity, prolong therapeutic levels and generate high drug concentrations at the tumor sites. Cumulatively, this would result in reduced systemic toxicity and enhanced drug efficacy.
Methods: Previous studies have shown that liposomes can serve as excellent carriers for otherwise poorly soluble ATRA. Delivery of ATRA to the lung tissue of mice was accomplished by nebulization of L-**ATRA**. The **liposomes** in the aerosol were relatively uniform (309 +/- 138 nm), stable, and retained the drug well. Results: The drug was effectively delivered at high concentrations (10 +/- 2 mu g/g of tissue) to the lungs of mice and was retained for at least up to 96 h after a single exposure to L-ATRA aerosol. No appreciable levels of ATRA were detected in the blood or the liver of treated mice. The aerosol-delivered ATRA was biologically active as demonstrated by its ability to induce the expression of tissue-type transglutaminase. Conclusion: Aerosol delivery of L-ATRA offers an effective way to deliver high levels of ATRA to the lung without apparent pulmonary toxic effects.

L19 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1989:520887 CAPLUS
DOCUMENT NUMBER: 111:120887
TITLE: Method of producing high aqueous volume multilamellar vesicles
INVENTOR(S): Wallach, Donald F. H.
PATENT ASSIGNEE(S): Micro-Pak, Inc., USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8806881	A1	19880922	WO 1988-US721	19880308 <--
W: AU, BB, BG, BR, DK, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, RO, SD, SU				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
US 4855090	A	19890808	US 1987-78658	19870728 <--
AU 8816836	A1	19881010	AU 1988-16836	19880308 <--
AU 603447	B2	19901115		
EP 349593	A1	19900110	EP 1988-904011	19880308 <--
EP 349593	B1	19911127		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
JP 02503646	T2	19901101	JP 1988-503735	19880308 <--
JP 06000193	B4	19940105		
AT 69723	E	19911215	AT 1988-904011	19880308 <--
CA 1289420	A1	19910924	CA 1988-561288	19880311 <--
CA 2062726	AA	19901227	CA 1990-2062726	19900613 <--
WO 9100084	A1	19910110	WO 1990-US3339	19900613 <--
W: AU, BR, CA, FI, HU, JP, NO, SU				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
AU 9059471	A1	19910117	AU 1990-59471	19900613 <--
US 5234767	A	19930810	US 1991-759732	19910912 <--
US 5474848	A	19951212	US 1994-200351	19940203 <--
US 5628936	A	19970513	US 1995-456283	19950531 <--

PRIORITY APPLN. INFO.:

US 1987-25525	A	19870313
US 1987-78658	A	19870728
US 1987-124824	A2	19871124
US 1988-157571	A2	19880303
EP 1988-904011	A	19880308
WO 1988-US721	A	19880308
US 1989-371738	A	19890626
US 1989-410647	B1	19890921
US 1989-443516	A1	19891129
WO 1990-US3339	A	19900613
US 1991-683835	B1	19910411
US 1992-944696	B1	19920914
US 1993-5940	B1	19930119

OTHER SOURCE(S): MARPAT 111:120887

AB The title vesicles are prepd. by combining a lipophilic phase with an excess of aq. phase, under high shear. The lipophilic phase is obtained by blending a polyoxyethylene alkyl ether or polyglycerol alkyl ether surfactant with a sterol and a charge-producing amphiphile, at a temp. above the m.p. of the surfactant. Amphiphilic or hydrophilic drugs and agrochems. may be encapsulated into the vesicles. A mixt. of polyoxyethylene cetyl ether 0.696, cholesterol 0.073 and dicetyl phosphate 0.055g was blended at 40.degree. into 10 mL 5 mM phosphate buffer (pH 7.4) contg. 150 mM NaCl, to give multilamellar vesicles.

L24 ANSWER 5 OF 15 PCTFULL COPYRIGHT 2003 Univentio on STN

ACCESSION NUMBER: 2001032145 PCTFULL ED 20020820

TITLE (ENGLISH): METHOD OF CANCER TREATMENT

TITLE (FRENCH): METHODE DE TRAITEMENT DU CANCER

INVENTOR(S): ANDREEFF, Michael;
ESTEY, Elihu, H.

PATENT ASSIGNEE(S): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001032145	A1	20010510

DESIGNATED STATES
W: CA JP AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 2000-US30042 A 20001030

PRIORITY INFO.: US 1999-09/431,547 19991029

L24 ANSWER 4 OF 15 PCTFULL COPYRIGHT 2003 Univentio on STN
ACCESSION NUMBER: 2001074384 PCTFULL ED 20020822
TITLE (ENGLISH): COMBINED **INTERFERON** ALFA AND **LIPOSOMAL**-ENCAPSULATED ALL-TRANS **RETINOIC ACID**, INCLUDING PREPARATION AND USE
TITLE (FRENCH): INTERFERON ALFA ET ACIDE ALL-TRANS RETINOIQUE LIPOSOMAL ENCAPSULE COMBINES, PREPARATION ET UTILISATION
INVENTOR(S): NANUS, David
PATENT ASSIGNEE(S): ARONEX PHARMACEUTICALS, INC.
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001074384	A1	20011011

DESIGNATED STATES
W: CA JP AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
APPLICATION INFO.: WO 2001-US9161 A 20010321
PRIORITY INFO.: US 2000-60/193,535 20000331
US 2001-09/811,346 20010316

L19 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:526816 CAPLUS
DOCUMENT NUMBER: 122:274066
TITLE: Biphasic multilamellar lipid vesicles
INVENTOR(S): Foldvari, Marianna
PATENT ASSIGNEE(S): University of Saskatchewan, Can.
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9503787	A1	19950209	WO 1994-CA409	19940728	<--
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN					
RW: KE, MW, SD, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
CA 2168260	AA	19950209	CA 1994-2168260	19940728	<--
AU 9473438	A1	19950228	AU 1994-73438	19940728	<--
EP 711148	A1	19960515	EP 1994-922214	19940728	<--
EP 711148	B1	20000830			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
AT 195866	E	20000915	AT 1994-922214	19940728	<--
ES 2152324	T3	20010201	ES 1994-922214	19940728	
US 5853755	A	19981229	US 1997-872068	19970610	<--
US 5993851	A	19991130	US 1998-42097	19980313	<--

PRIORITY APPLN. INFO.:			
US 1993-98102	A	19930728	
WO 1994-CA409	W	19940728	
US 1995-507923	B1	19950727	
US 1997-872068	A3	19970610	

AB A biphasic multilamellar lipid vesicle comprising a plurality of spaced apart lipid bilayers that include a liposome-forming component and optionally a biol. active agent entrapped within the lipid bilayers. The lipid vesicle also comprises peripheral aq. soln. compartments formed between the lipid bilayers and a central lipophilic core compartment substantially at the center of the multilamellar lipid vesicle.

L10 ANSWER 6 OF 13 CANCERLIT
ACCESSION NUMBER: 1998643203 CANCERLIT
DOCUMENT NUMBER: 98643203
TITLE: **Retinoic** acid receptor-beta (RAR-beta) expression in renal cell carcinoma (RCC) of patients treated with **interferon** alfa-2a (IFN) and 13-cis-**retinoic** acid (CRA): correlation with clinical response (Meeting abstract).
AUTHOR: Leung A C F; **Nanus D M**; Mazumdar M; Brown K T; Lotan R; Xu X C; Reuter V E; Motzer R J
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center (MSKCC), New York NY.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, **(1997)** 16 A1203.
ISSN: 0732-183X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109

AB A phase II trial of IFN and CRA conducted in pts with advanced RCC at MSKCC resulted in a 30% major response proportion. Augmentation of the antiproliferative effect of IFN on RCC cells by CRA was demonstrated in vitro and the data suggested the CRA effect may be mediated through RAR-beta (Clin Cancer Res; 2:1077, 1996). The goal of this study was to correlate clinical response with tumor expression of RAR-beta. Tumor specimens obtained prior to and/or during therapy for patients treated on the phase II trial were analyzed for RAR-beta expression. RAR-beta expression was measured by in situ hybridization (Diag Mol Pathol; 3:122, 1994). Levels of expression were based on staining-intensity scores as follows: low = absent or weak intensity staining, high = strong intensity staining. Major clinical response = over 50% reduction in tumor size. A relationship was not observed between pre-therapy level and clinical response in 23 pts with tumors studied. However, there was a correlation between change in expression of RAR-beta measured before and during therapy and clinical response (p=0.09). In 9 pts. with tumor specimens obtained before and during IFN/CRA treatment, an increase in RAR-beta expression was observed in 4 pts, all of whom experienced a major clinical response. In contrast, only 1/5 pts with no increase in expression had a major clinical response. These data suggest that upregulation of RAR-beta is associated with clinical response to IFN/CRA therapy in RCC.

L10 ANSWER 7 OF 13 CANCERLIT
ACCESSION NUMBER: 1998643162 CANCERLIT
DOCUMENT NUMBER: 98643162
TITLE: Clinical studies of 13-cis-**retinoic** acid (CRA) in patients with metastatic renal cell carcinoma (RCC) (Meeting abstract).
AUTHOR: Berg W J; Schwartz L; Amsterdam A; Mazumdar M; **Nanus D M**; Motzer R J
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, NY, NY.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, **(1997)** 16 A1162.
ISSN: 0732-183X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109

AB A phase II trial of **interferon**-alpha-2A (IFN) combined with CRA suggested that CRA increased the response rate of IFN in RCC (J Clin Oncol; 13:1950, 1995). The antitumor effect of CRA, independent of IFN, was evaluated in a phase II trial. 25 patients (pts) with RCC were treated with CRA alone at 1 mg/kg/day orally. No pt achieved a CR or PR, and 8 had stable disease for over 3 months. Moreover, the response data for the phase II trial of CRA and IFN was updated. The median duration of response among the 13 pts. (30% of 43) that achieved a PR or CR was 22 months, compared to 12 months in our prior experience with IFN (J Clin Oncol 11:1368, 1993). Two pts remain free of disease at 38+ and 44+ months, and one pt who relapsed in CR off treatment has achieved a PR to re-treatment with CRA and IFN. In conclusion, CRA added to IFN in the treatment of RCC appears to increase both the rate and duration of response, but as a single agent CRA did not show antitumor activity. The relative benefit of adding CRA to IFN is being addressed in a randomized phase III trial.

L10 ANSWER 11 OF 13 CANCERLIT
ACCESSION NUMBER: 95609398 CANCERLIT
DOCUMENT NUMBER: 95609398
TITLE: Analysis of 13-cis **retinoid** acid induced antiproliferative effects alone and in combination with **interferon**-alpha in human prostate cancers (Meeting abstract).
AUTHOR: Bogenrieder T; Papandreou C; Hoffman A D; Chen G; Steckelman E A; Kelly W K; Scher H I; Albino A P; **Nanus D M**
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY 10021.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1995)** 36 A1621.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950906
Last Updated on STN: 19970509

AB Androgen independent prostate cancers are resistant to most chemotherapeutic and biologic therapies. Recent studies have shown that the addition of 13-cis **retinoid** acid (CRA) to **interferon** -alpha (IFN-alpha) resulted in greater antitumor activity in the treatment of patients with a number of epithelial malignancies. We investigated the antiproliferative effects of CRA alone and in combination with IFN-alpha in the androgen independent prostate cancer cell lines PC-3 and DU 145, and the neuroendocrine prostate cancer cell line TSU-Pr1. Cells were plated in triplicate wells and growth assays were performed over 7 days on two separate occasions. Cell numbers were determined on Day 7 using a Coulter counter. Percent inhibition is in comparison to untreated controls. PC-3 and DU 145 cells were moderately growth inhibited (30%) and TSU-Pr1 cells were resistant to CRA at a concentration of 10(-6)M. IFN-alpha at concentrations of 10, 100 and 1000 U/ml caused a dose-dependent inhibition in cell growth in all three cell lines. Maximal effect was observed at 1000 U/ml with 43% and 46% growth inhibition of DU 145 and TSU-Pr1, respectively, and 79% inhibition of PC-3 cells. The addition of CRA to IFN-alpha did not result in greater antiproliferative action in any cell line as compared to IFN-alpha alone, even at a concentration of 10(-6)M CRA. These data indicate that androgen-independent prostate cancers exhibit only moderate sensitivity to the antiproliferative effects of CRA, but do exhibit a dose-dependent response to the antiproliferative effects of IFN-alpha. Furthermore, CRA does not augment the antiproliferative effects which result from IFN-alpha alone.

L10 ANSWER 9 OF 13 CANCERLIT
ACCESSION NUMBER: 95610808 CANCERLIT
DOCUMENT NUMBER: 95610808
TITLE: The antiproliferative effects of **retinoic** acid is mediated through the **retinoic** acid receptor beta in human renal cell carcinoma cell lines (Meeting abstract).
AUTHOR: Hoffman A D; Bogenrieder T; Steckelman E; Loganzo F; Papandreou C; Schacher Y; Albino A P; **Nanus D M**
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY 10021.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1995)** 36 A3035.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950809
Last Updated on STN: 19970509

AB 13-cis-**retinoic** acid (RA) augments the antitumor effects of **interferon**-alpha (IFN) in patients with renal cell carcinoma (RC; Proc ASCO 13:713, 1994). **Retinoid** effects are mediated through **retinoic** acid nuclear receptors (RARs) which are ligand-regulated transcriptional factors. Following RA binding, the RARs transactivate the expression of other genes which presumably direct the synthesis of proteins that promote differentiation and inhibit cell growth. We determined the antiproliferative effects of RA on 12 RC cell lines and correlated this with the expression of RAR-alpha and -beta. 11/12 cell lines which were either resistant or only moderately inhibited by RA did not express RAR-beta constitutively as determined by Northern analysis; moreover, in these cells RA treatment did not induce expression of RAR-beta. In contrast, 1/12 cell lines (SK-RC-06) was greater than 90% inhibited by RA and these cells expressed constitutive levels of RAR-beta.

Furthermore, RAR-beta-specific MRNA was upregulated by RA treatment. In contrast, RAR-alpha transcripts were abundant in all 12 cell lines examined and were not affected by RA treatment. The addition of IFN to RA in SK-RC-06 cells and 2 RA-resistant cell lines resulted in an increased antiproliferative effect compared to either drug alone, but did not affect the level of RAR expression. These data suggest that (1) the majority of RC cell lines are resistant to RA, (2) resistance correlates with repressed expression of RAR-beta mRNA, and (3) the antiproliferative effects of RA on RC cells may be mediated through RAR-beta. Transfection experiments of RA resistant cell lines with an expression vector containing RAR-beta are in progress to determine its effect on RC cells.

L31 ANSWER 32 OF 41 USPATFULL on STN
ACCESSION NUMBER: 1998:88875 USPATFULL
TITLE: Regulating gene expression using **retinoids** with Ch.sub.2 OH or related groups at the side chain terminal position
INVENTOR(S): Gudas, Lorraine J., New York, NY, United States
Achkar, Charles, North Bergen, NJ, United States
Buck, Jochen, New York, NY, United States
Langston, Alexander W., New York, NY, United States
Derguini, Fadila, New York, NY, United States
Nakanishi, Koji, New York, NY, United States
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., Ithaca, NY, United States (U.S. corporation)
The Trustees of Columbia University in the City of New York, New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 5786391		19980728		
APPLICATION INFO.:	US 1995-371535		19950111	(8)	<--

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Goldberg, Jerome D.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 3
NUMBER OF DRAWINGS: 18 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 1105
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Regulating gene expression using **retinoids** with Ch.sub.2 OH or related groups at the side chain terminal position
AI US 1995-371535 19950111 (8) <--
AB For the first time, certain **retinoids** with a side chain terminal CH.sub.2 OH group or ester or ether thereof or aldehyde rather than a side chain. . . psoriasis and photodamaged or aging skin. These compounds have stability and in vitro half-life advantages over and solubility differences from all-trans-**retinoic acid** and activity advantages over 13-cis **retinoic acid**.
SUMM . . . useful in the treatment of squamous cell carcinoma of the cervix and of the skin, when used in combination with a-**interferon**. See Lippman, S. M., et al (10) and Lippman, S. M., et al (11).
DETD . . . include a therapeutically effective amount of retinoid herein and pharmaceutically acceptable carrier such as sterile water or physiological saline, and **liposome** delivery systems can be used to accommodate for lack of solubility.
DETD . . . be employed alone or in combination therapy including but not limited to combination therapy with biological response modifiers, such as **interferons**; growth factors; vitamins; hormones; intracellular signalling molecules such as cyclic AMP; cytotoxic cancer chemotherapeutic drugs; other retinoids, such as all-trans-retinoic. . .
DETD . . . Paredes-Espinoza, M., Delgadillo-Madrueno, F., Paredes-Casillas, P., Hong, W. K., Holdener, E., and Krakoff, I. H. (1992) 13-cis retinoic acid plus **interferon .alpha**.-2a: highly active systemic therapy for squamous cell carcinoma of the cervix. J. Natl. Cancer Inst. 84: 241-245.
DETD . . . D. M., Schusterman, M. A., Krakoff, I. H., Gutterman, J. U., and Hong, W. K. (1992) 13-cis retinoic acid and **interferon . alpha**.-2a: effective combination therapy for advanced squamous cell carcinoma of the skin. J. Natl. Cancer Inst. 84: 235-241.

L25 ANSWER 10 OF 17 USPATFULL
ACCESSION NUMBER: 2002:22535 USPATFULL
TITLE: PROCESS FOR PRODUCING ARSENIC TRIOXIDE FORMULATIONS AND
METHODS FOR TREATING CANCER USING ARSENIC TRIOXIDE OR MELARSOPROL
INVENTOR(S): WARRELL, RAYMOND P., JR., WESTFIELD, NJ, UNITED STATES
PANDOLFI, PIER PAOLO, NEW YORK, NY, UNITED STATES
GABRILOVE, JANICE L., NEW YORK, NY, UNITED STATES

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2002013371	A1	20020131		
APPLICATION INFO.:	US 1998-189965	A1	19981110	(9)	<--

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-64655P	19971110 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
LINE COUNT: 1391
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 1998-189965 A1 19981110 (9) <--
AB . . . lymphoma and solid tumors. Further, the arsenic compounds may be used in combination with other therapeutic agents, such as a **retinoid**. The invention also provides a process for producing arsenic trioxide formulations.
SUMM . . . compositions suitable for topical or transdermal delivery, including but not limited to iontophoretic methods. Specific therapeutic regimens, pharmaceutical compositions, and **kits** are also provided by the invention.
SUMM . . . floxuridine, methotrexate, vincristine, vinblastine, taxol, etoposide, temiposide, dactinomycin, daunorubicin, doxorubicin, bleomycin, mitomycin, cisplatin, carboplatin, estramustine phosphate, hydroxyurea, BCNU, procarbazine, VM-26, **interferons**, and all-trans retinoic acid (ATRA), or other retinoids (See, for example, the Physician Desk References 1997). In addition, the arsenic. . . .
SUMM [0068] The invention also provides **kits** for carrying out the therapeutic regimens of the invention. Such **kits** comprise in one or more containers therapeutically effective amounts of the arsenic compounds in pharmaceutically acceptable form. The arsenic compound. . .

L32 ANSWER 14 OF 72 MEDLINE DUPLICATE 5

ACCESSION NUMBER: 97303870 MEDLINE
DOCUMENT NUMBER: 97303870 PubMed ID: 9160172
TITLE: Clinical pharmacokinetics of tretinoin.
AUTHOR: Regazzi M B; Iacona I; Gervasutti C; Lazzarino M; Toma S
CORPORATE SOURCE: Department of Pharmacology, IRCCS-S, Matteo Hospital, Pavia, Italy.
SOURCE: CLINICAL PHARMACOKINETICS, **(1997 May)** 32 (5) 382-402. Ref: 111
Journal code: 7606849. ISSN: 0312-5963.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970813
Last Updated on STN: 19970813
Entered Medline: 19970804

AB Recent reports of the dramatic antitumour effect of tretinoin (all-trans retinoic acid) in patients with acute promyelocytic leukaemia (APL) have generated a great deal of interest in the use of this drug as a chemopreventive and therapeutic agent. However, the biological efficacy of tretinoin is greatly impaired by (presumably) an induced hypercatabolism of the drug leading to reduced tretinoin sensitivity and resistance. Several pharmacokinetic studies have shown that plasma drug exposure [as measured by the plasma area under the concentration-time curve (AUC **infinity**)] declines substantially and rapidly when the drug is administered in a long term daily tretinoin regimen. These observations led to the hypothesis that the rapid development of acquired clinical resistance to tretinoin may have a pharmacological basis and result from an inability to present an effective drug concentration to the leukaemic cells during continuous treatment. The principal mechanisms proposed to explain the increased disappearance of tretinoin from plasma include: (i) decreased intestinal absorption; (ii) enhanced enzymatic catabolism; and (iii) the induction of cytoplasmic retinoic acid binding proteins (CRABP), which leads to increased drug sequestration. The most favoured explanation is that continuous tretinoin treatment acts to induce drug catabolism by cytochrome P450 (CYP) enzymes. Several strategies aimed at preventing or overcoming induced tretinoin resistance have been, and are being, planned. These strategies include intermittent dose administration, administration of pharmacological inhibitors of CYP oxidative enzymes, combination with **interferon**-alpha and intravenous administration of **liposome**-encapsulated **tretinoin**. As these strategies are now under investigation and the number of patients enrolled is small, further studies are needed to determine the efficacy and toxicity of these new schedules of drug administration. In this article we provide an overview of the relevant aspects of tretinoin physiology and pharmacokinetics, and summarise the current status of knowledge to help in the better optimisation of tretinoin administration.

Int J Cancer 1997 Feb 7;70(4):481-3

Related Articles,

Links

Retinoid-interferon therapy of solid tumors.

Lippman SM, Lotan R, Schleuniger U.

Department of Clinical Cancer Prevention, University of Texas, M.D. Anderson Cancer Center, Houston 77030, USA.

Publication Types:
Review
Review, Tutorial

PMID: 9033661 [PubMed - indexed for MEDLINE

J Interferon Cytokine Res 1996 Jul;16(7):489-99

Related Articles,

Links

The biologic activity and molecular characterization of a novel synthetic interferon-alpha species, consensus interferon.

Blatt LM, Davis JM, Klein SB, Taylor MW.

Amgen Inc., Thousand Oaks, CA 91230, USA.

Consensus interferon (Infergen) is a wholly synthetic type I interferon (IFN), developed by scanning several interferon-alpha nonallelic subtypes and assigning the most frequently observed amino acid in each position, resulting in a consensus sequence. The antiviral, antiproliferative, NK cell activation activity, cytokine induction, and interferon-stimulated gene-induction activity of consensus interferon has been compared with naturally occurring type I interferons. In all of these comparisons, consensus interferon had a higher activity when compared, on a mass basis, with IFN-alpha 2a and IFN-alpha 2b, although the activity was the same for all of these parameters on an antiviral unit basis. That a synthetic type I interferon could have higher activities than naturally occurring molecules is surprising and may be a result of the higher affinity for the array of type I interferon receptors demonstrated for consensus interferon when compared with IFN-alpha. In contrast, consensus interferon was shown to be an inferior inducer of IL-1 beta when compared with IFN-alpha. These results may reflect differential binding to multiple accessory proteins interacting with a type I interferon receptor. These unique biologic properties may lead to a favorable clinical benefit for consensus interferon when compared with the naturally occurring recombinant molecules. Ongoing clinical trials will ascertain whether consensus interferon can be used in a wide array of disease situations, such as chronic viral infections and certain malignancies.

Rev Immunogenet 2000;2(3):374-86

Interferon activation and innate immunity.

Le Page C, Genin P, Baines MG, Hiscott J.

Terry Fox Molecular Oncology Group, Lady Davis Institute for Medical Research, Montreal, Canada.

The interferons are a family of cytokine mediators critically involved in alerting the cellular immune system to viral infection of host cells. Interferons not only exhibit important antiviral effects but also exert a key influence on the quality of the cellular immune responses and amplify antigen presentation to specific T cells. Type I interferon (IFN-alpha and IFN-beta) is secreted by virus-infected cells while type II, immune or gamma interferon (IFN-gamma) is mainly secreted by T cells, natural killer (NK) cells and macrophages. Interferons interact with specific cellular receptors, which promote production of second messengers ultimately leading to expression of antiviral and immune modulatory genes. The IFN genes themselves are regulated by transcriptional and posttranscriptional mechanisms including modulation by a family of interferon regulatory factors (IRFs) synthesised by host cells. IFNs activate macrophages, induce B cells to switch immunoglobulin type, alter T helper response, inhibit cell growth, promote apoptosis and induce an antiviral state in uninfected cells. The therapeutic potential of the IFNs is currently the focus of intense attention in a number of virus-associated diseases, tumours and autoimmune disorders.

Cancer Treat Res 1998;94:23-33

Interferon use in solid tumors.

John WJ, Foon KA.

Lucille P. Markey Cancer Center, University of Kentucky, Lexington 40536, USA.

Publication Types:
Review
Review, Academic

PMID: 9587680 [PubMed - indexed for MEDLINE]

(FILE 'HOME' ENTERED AT 15:26:01 ON 01 MAR 2003)

FILE 'MEDLINE, BIOSIS, CANCERLIT, LIFESCI, BIOTECHDS, CAPLUS' ENTERED AT 15:26:26 ON 01 MAR 2003

```
L1           461 S NANUS?/AU
L2       1610865 S INTERFERON? OR INF OR INFA?
L3            16 S AINF
L4       1610875 S L2 OR L3
L5            82 S L1 AND L4
L6         94869 S RETINOI? OR ISOTRETINOIN OR TRETINOIN OR ATRAGEN# OR INTON#
L7            54 S L1 AND L6
L8            36 S L5 AND L7
L9            28 S L8 AND PY<2001
L10           13 DUP REM L9 (15 DUPLICATES REMOVED)
L11      8849616 S INTERFERON# OR INF? OR AINF? OR BINF? OR GINF? OR ALPHAINF?
O
L12       102388 S RETINOI? OR ACITRETIN# OR ETRETINATE# OR FENRETINIDE# OR
RETI
L13           71 S ATRAGEN# OR (INTON(W)A#) OR INTONA#
L14         3059 S L12 AND LIPID?
L15           22 S L11 AND L13
L16          578 S L11 AND L14
L17          573 S L12(5A)LIPID?
L18           93 S L11 AND L17
L19           58 S L11(S)L17
L20           80 S L19 OR L15
L21           61 S L20 AND PY<2001
L22           36 DUP REM L21 (25 DUPLICATES REMOVED)
L23        88947 S PANRETIN# OR (VIT?(W)A) OR VITA
L24         3357 S L23(S)(LIPID? OR LIPOSOM?)
L25         1432 S L23(5A)(LIPID? OR LIPOSOM?)
L26          277 S L12(5A)LIPOSOM?
L27          112 S L11(S)L25
L28           37 S L11(S)L26
L29          149 S L27 OR L28
L30          137 S L29 NOT L20
L31          106 S L30 AND PY<2001
L32           72 DUP REM L31 (34 DUPLICATES REMOVED)
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FILE 'PCTFULL, USPATFULL, EUROPATFULL' ENTERED AT 16:25:35 ON 01 MAR 2003

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L33        26290 S RETINOID# OR ACITRETIN OR ETRETINATE OR FENRETINIDE OR
ISOTRE
L34          389 S L33(3A)(LIPOSOM? OR LIPID?)
L35           27 S ATRAGEN# OR (INTONA#) OR (INTON(W)A#)
L36        71170 S INTERFERON# OR INF OR INFA## OR INFB## OR INFG## OR
INFALPHA#
L37           16 S L36 AND L35
L38          124 S L36 AND L34
L39         5450 S L36/TI,AB
L40           20 S L34/TI,AB
L41            4 S L39 AND L34
L42            8 S L40 AND L36
L43           14 S L34(S)L36
L44           31 S L37 OR L41 OR L42 OR L43
L45            6 S L44 AND AD<20000331
L46            5 S L44 AND PD<20000331
L47            6 S L45 OR L46
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L10 ANSWER 10 OF 13 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 95363477 MEDLINE
DOCUMENT NUMBER: 95363477 PubMed ID: 7636535
TITLE: **Interferon** alfa-2a and 13-cis-**retinoic** acid in renal cell carcinoma: antitumor activity in a phase II trial and interactions in vitro.
AUTHOR: Motzer R J; Schwartz L; Law T M; Murphy B A; Hoffman A D; Albino A P; Vlamis V; **Nanus D M**
CORPORATE SOURCE: Department of Medical Imaging, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.
CONTRACT NUMBER: CA-05826 (NCI)
CA-57475 (NCI)
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, **(1995 Aug)** 13 (8) 1950-7.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950921
Last Updated on STN: 19970203
Entered Medline: 19950911

AB PURPOSE: A phase II trial of **interferon** alfa-2a (IFN) and 13-cis-**retinoic** acid (CRA) was conducted in patients with renal cell carcinoma (RCC). In vitro studies were performed to investigate potential mechanisms of interaction. PATIENTS AND METHODS: Forty-four patients were treated. IFN was given daily at 3 MU and escalated to 6 and 9 MU if tolerated. The dose of CRA was 1 mg/kg/d. The effects of combining CRA and IFN on the proliferation of five RCC cell lines were examined, and **retinoid** sensitivity was correlated to the expression of **retinoic** acid receptors. RESULTS: Thirteen (30%) of 43 assessable patients achieved a major response (three complete and 10 partial). Responding sites included bone metastases and renal primary tumors. Seven responding patients remain progression-free at 10+ to 19+ months. The response proportion was higher than in our prior experience with IFN, which was 10% in 149 patients. Eleven of 12 renal cancer cell lines were resistant to CRA alone; one, SK-RC-06, showed 90% inhibition of cell growth. CRA augmented the antiproliferative effect of IFN in several IFN-sensitive cell lines, but not in IFN-resistant lines. Northern blot analysis showed that expression of **retinoic** acid receptor-beta (RAR-beta) was repressed and not induced by **retinoic** acid in **retinoic** acid-insensitive RCC lines. However, RAR-beta expression was induced by **retinoic** acid in SK-RC-06 cells. CONCLUSION: IFN and CRA showed antitumor activity in patients with advanced RCC, and the proportion and nature of response suggested CRA added therapeutic benefit to IFN. A phase III randomized trial of IFN plus CRA versus IFN alone and a phase II trial of single-agent CRA have been initiated.

L10 ANSWER 8 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:194189 BIOSIS
DOCUMENT NUMBER: PREV199799493392
TITLE: Analysis of **retinoid** acid receptor beta (RAR-beta) expression, angiogenesis and apoptosis in tumor specimens from patients with renal cell carcinoma treated with **interferon** alfa-2A and 13-cis-**Retinoic** Acid: Correlation with response.
AUTHOR(S): **Nanus, David M. (1)**; Leung, Abraham; Hutchinson, Brian; Brown, Karen T.; Lotan, Reuben; Reuter, Victor E.; Motzer, Robert J.
CORPORATE SOURCE: (1) New York, NY USA
SOURCE: Journal of Urology, (1997) Vol. 157, No. 4 SUPPL., pp. 277.

Meeting Info.: 92nd Annual Meeting of the American Urological Association New Orleans, Louisiana, USA April 12-17, 1997
ISSN: 0022-5347.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L10 ANSWER 5 OF 13 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999357136 MEDLINE
DOCUMENT NUMBER: 99357136 PubMed ID: 10430067
TITLE: Up-regulation of **retinoic** acid receptor beta expression in renal cancers in vivo correlates with response to 13-cis-**retinoic** acid and **interferon**-alpha-2a.
AUTHOR: Berg W J; **Nanus D M**; Leung A; Brown K T; Hutchinson B; Mazumdar M; Xu X C; Lotan R; Reuter V E; Motzer R J
CORPORATE SOURCE: Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
CONTRACT NUMBER: CA 57475 (NCI)
SOURCE: CLINICAL CANCER RESEARCH, **(1999 Jul)** 5 (7) 1671-5.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990922

AB **Retinoic** acid receptor-beta (RAR-beta) mRNA is not expressed by **retinoid**-resistant renal cancer cell lines but is present in **retinoid**-sensitive SK-RC-06 renal cancer cells and increases following incubation with **retinoic** acid (RA), suggesting that the antitumor action of RA is mediated through RAR-beta (A. D. Hoffman et al., Clin. Cancer Res., 2: 1077-1082, 2996). To determine whether RAR-beta expression correlates in vivo with major clinical response to patients with renal cell carcinoma (RCC) who were treated with **retinoid**-based therapy, we used in situ hybridization to analyze RAR-beta expression in tumor specimens obtained from patients who were treated on a clinical trial with 13-cis-RA and IFN-alpha. Thirty-three tissue specimens were analyzed (23 pretreatment and 10 on-treatment). mRNA expression was based on staining intensity, with scores within tumor cells ranging from 0 to 2, where a score of 0 indicated absence of staining, a score of 1 indicated weak staining, and a score of 2 indicated strong staining. RAR-beta expression was present in 22 of 23 (96%) pretreatment and 9 of 10 (90%) on-treatment specimens. Pretreatment levels of expression did not associate with the site of biopsy and did not predict for major clinical response to RA plus IFN-alpha therapy (two-sided Fisher's exact test, P = 0.826). However, an increase in the intensity of RAR-beta mRNA expression was detected in four of five (80%) patients who achieved a major response but in none of the five patients with progressive disease in whom sequential biopsies were available (two-sided Fisher's exact test, P = 0.048). These data show that RAR-beta transcripts increase in tumor cells of RCC patients who clinically respond to **retinoid**-based therapy. **Retinoids** that potently induce RAR-beta expression

should be evaluated in the treatment of advanced RCC.

L32 ANSWER 4 OF 72 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:191808 CAPLUS
DOCUMENT NUMBER: 130:213577
TITLE: Aerosol delivery of liposomal all-trans-retinoic acid to the lungs
AUTHOR(S): Parthasarathy, Ranjani; Gilbert, Brian; Mehta, Kapil
CORPORATE SOURCE: Dep. Endocrinology, Anderson Cancer Center, Univ. Texas, Houston, TX, USA
SOURCE: Cancer Chemotherapy and Pharmacology (**1999**), 43(4), 277-283
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Vehiculating of all-trans-retinoic acid (ATRA) in liposomes (L-ATRA) and delivering it via aerosol to lung was examd. in mice. The drug was effectively delivered at high concns. (10 .mu.g/g of tissue) to the lungs and was retained .ltoreq.96 h after a single exposure to L-ATRA aerosol. The aerosol-delivered ATRA proved biol. active.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L10 ANSWER 4 OF 13 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000229089 MEDLINE
DOCUMENT NUMBER: 20229089 PubMed ID: 10768602
TITLE: Novel investigative approaches for advanced renal cell carcinoma.
AUTHOR: Berg W J; Divgi C R; **Nanus D M**; Motzer R J
CORPORATE SOURCE: Department of Nuclear Medicine, Weill Medical College of Cornell University, New York, NY, USA.
SOURCE: SEMINARS IN ONCOLOGY, **(2000 Apr)** 27 (2) 234-9.
Ref: 59
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000424

AB Metastatic renal cell carcinoma remains one of the most treatment-resistant malignancies in humans. As such, long-term survival is limited to a minority of patients. **Interferon**-alpha and interleukin-2 induced major responses in some patients with renal cell carcinoma, and in so doing generated a great deal of interest and hope. However, clinical benefit is limited to relatively few patients. Here, we briefly discuss the management of metastatic renal cell carcinoma, and then elaborate on several novel treatment approaches in development, including **retinoids**, monoclonal antibodies, and antiangiogenesis strategies.

L10 ANSWER 2 OF 13 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000203749 MEDLINE
DOCUMENT NUMBER: 20203749 PubMed ID: 10741705
TITLE: The development of biologic end points in patients treated with differentiation agents: an experience of **retinoids** in prostate cancer.
AUTHOR: Kelly W K; Osman I; Reuter V E; Curley T; Heston W D; **Nanus D M**; Scher H I
CORPORATE SOURCE: Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
CONTRACT NUMBER: CA-05826 (NCI)
DK/CA 47650 (NIDDK)
SOURCE: CLINICAL CANCER RESEARCH, **(2000 Mar)** 6 (3) 838-46.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000613
Last Updated on STN: 20000613
Entered Medline: 20000601

AB The evaluation of new therapies in prostate cancer requires unique end points for agents with diverse mechanisms of action. Because **retinoic** acid may have a confounding effect on prostate-specific antigen, we incorporated a pathological end point into the outcome assessment of two sequential clinical trials using all-trans-**retinoic** acid (ATRA) and the combination of 13-cis-**retinoic** acid and IFN-2a (cRA IFN). Pre- and posttherapy tumor biopsy specimens were studied for histological changes, apoptosis (terminal deoxynucleotidyl transferase-mediated nick end labeling assay), and proliferation index (Ki67). Prostate-specific membrane antigen (PSMA) expression was also evaluated using two different monoclonal antibodies to its intracellular domain (Cytogen 7E11 and Hybritech PM2). Fourteen patients with androgen-independent disease were treated with ATRA (50 mg/m2 p.o. every 8 h daily) and 16 androgen-independent and 4 androgen-dependent patients were treated with cRA IFN (10 mg/kg/day cRA plus 3, 6, or 9 million units daily IFN). Both therapies were well tolerated, with fatigue and cheilitis being the most common adverse events. Clinical activity, assessed by radiographs and serum prostate-specific antigen, was minimal, and the majority of patients progressed within 3 months. One patient with androgen-dependent disease had prolonged stabilization for >1 year. The majority of cases (95%) showed no gross histological changes and no difference in apoptotic or proliferative indices. Increased PSMA immunoreactivity was seen in seven of nine (78%) cases using PM2 antibody and in two of nine (22%) cases using the 7E11 antibody. Although antitumor effects were modest, the results suggest a role for **retinoids** in modulating the expression of PSMA on prostate cancer cells.

L22 ANSWER 12 OF 36 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:376947 BIOSIS
DOCUMENT NUMBER: PREV199800376947
TITLE: A multicenter, phase II/III study of **atragen** (Tretinoin liposomal) in patients with AIDS-associated Kaposi's sarcoma.
AUTHOR(S): Bernstein, Zale P.; Rios, Adan; Scadden, David; Groopman, Jerome; Northfelt, Donald; Lang, William; Fischl, Margaret;
Cohen, Philip; Bock, Amy; Gill, Parkesh
CORPORATE SOURCE: Roswell Park Cancer Inst., George Washington Univ., Oncol. Med. Associates, ViRx, Univ. Miami, New England Deacones, Genyzme Corp., Norris Cancer, Coral Gables, FL USA
SOURCE: Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, (**April 1, 1998**) Vol. 17, No. 4, pp. A24.
Meeting Info.: Second National AIDS Malignancy Conference Bethesda, Maryland, USA April 6-8, 1998 National Cancer Institute
. ISSN: 1077-9450.
DOCUMENT TYPE: Conference
LANGUAGE: English

L22 ANSWER 7 OF 36 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1

ACCESSION NUMBER: 2000:222118 BIOSIS
DOCUMENT NUMBER: PREV200000222118
TITLE: The nonclinical safety evaluation of the anticancer drug **ATRAGEN**(R) (liposomal all-trans-retinoic acid.
AUTHOR(S): Wallace, Thomas L. (1); Larson, Jeffrey L.; Bazemore, Scott A.; Wilson, Chris W.; Cossum, Paul A.
CORPORATE SOURCE: (1) Aronex Pharmaceuticals, 8707 Technology Forest Place, The Woodlands, TX, 77381 USA
SOURCE: International Journal of Toxicology, (**Jan. Feb.**, **2000**) Vol. 19, No. 1, pp. 33-42.
ISSN: 1091-5818.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **ATRAGEN**(R) is a liposome-encapsulated intravenous (IV) formulation of the anticancer drug all-trans-retinoic acid (tretinoin). Retinoids as a class of compounds produce a characteristic profile of toxicities collectively known as hypervitaminosis A. As part of the nonclinical regulatory submission, it was important to determine if liposome encapsulation of tretinoin would change the expected profile of toxicities. To this end, a single-dose study in rats and repeated-dose 28-day studies in rats and dogs were conducted. In the single-dose study, **ATRAGEN** was given as a single IV bolus via the tail vein at dosages of 5, 20, or 80 mg/kg. In the first repeated-dose studies in rats, **ATRAGEN** was given by tail vein **infusion** at dosages of 2.5, 15, or 25 mg/kg/day and in the second, at dosages of 1, 10 or 10 mg/kg/day. The second study in rats also included a group given free tretinoin at a dose of 10 mg/kg/day; lowered to 1 mg/kg/day. **ATRAGEN** was given to dogs as an IV **infusion** in the cephalic or saphenous vein at dosages of 2.5, 5, or 10 mg/kg/day. **ATRAGEN** was not acutely toxic in rats at doses of 5 or 20 mg/kg, whereas deaths were seen at 80 mg/kg. In contrast, free tretinoin at a dosage of 10 mg/kg caused the deaths of most male rats after the first dose in the repeated-dose study; consequently, the dose was lowered to 1 mg/kg/day for remaining males and all females in that study. In the 28-day repeated-dose studies, minimal toxicities were observed in either rats or dogs at **ATRAGEN** doses of 2.5 mg/kg/day or less. Both free tretinoin and **ATRAGEN** at 1 mg/kg/day were without signs of hypervitaminosis A in rats. Moderate to marked retinoid-associated hypervitaminosis A was observed in the 28-day rats studies in the dose range of 10 to 25 mg/kg/day. In dogs, repeated administration of **ATRAGEN** of 5 or 10 mg/kg/day also led to moderate to marked hypervitaminosis A. In both species, hypervitaminosis A was manifested primarily as bone and testicular toxicities. In bone, premature closure of epiphyseal growth plates and/or a decrease in the activity of cells in the growth plate were seen. Loss of the cartilaginous growth plate and replacement with less dense trabecular bone resulted in weakened bones, most evident in rats. Rats had increased levels of serum alkaline phosphatase (ALP) and bone fractures were common with **ATRAGEN** doses of 10 mg/kg/day and higher. In addition to effects on bone growth,

endosteal fibroplasia, exostosis, and periosteal hemorrhages were observed in dogs. In both species, diffuse testicular atrophy, degenerative spermatic elements, and loss of seminiferous epithelium in the epididymis were observed microscopically. Hepatic enzyme levels were increased in rats, but no histopathological correlate was identified. Moderate to moderately severe nephrosis exemplified by a loss and/or degeneration of the kidney tubules was seen in dogs given 5 or 10 mg/kg/day. There was an increased weight of the spleens in rats receiving high dose volumes of liposomes; that is, control rats receiving empty liposomes and in rats receiving **ATRAGEN** in large dose volumes to provide tretinoin at dosages of 10 mg/kg/day and greater. Microscopically, there was an accumulation of macrophages with prominent vacuoles in the spleens of these rats. This effect on the spleen was not considered a pathological process but a clearance of liposomal material from the circulation by phagocytosis. No other toxicities were observed. Thus, these nonclinical safety studies of **ATRAGEN** conducted in rats or dogs found no unique toxicities from those observed previously in laboratory animals given tretinoin or other retinoids.

motivation?

L22 ANSWER 8 OF 36 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998325428 MEDLINE
DOCUMENT NUMBER: 98325428 PubMed ID: 9660998
TITLE: Differences in the lipoprotein distribution of free and liposome-associated all-trans-retinoic acid in human, dog, and rat plasma are due to variations in lipoprotein lipid and protein content.
AUTHOR: Wasan K M; Ramaswamy M; Ng S P; Wong W; Parrott S C; Ojwang J O; Wallace T; Cossum P A
CORPORATE SOURCE: Division of Pharmaceutics and Biopharmaceutics, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada.. Kwasan@unixg.ubc.ca
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AB The objective of the proposed study was to determine the distribution in plasma lipoprotein of free all-trans retinoic acid (ATRA) and liposomal ATRA (**Atragen;** composed of dimyristoyl phosphatidylcholine and soybean oil) following incubation in human, rat, and dog plasma. When ATRA and **Atragen** at concentrations of 1, 5, 10, and 25 micrograms/ml were incubated in human and rat plasma for 5, 60, and 180 min, the majority of the tretinoin was recovered in the lipoprotein-deficient plasma fraction. However, when ATRA and Afragen were incubated in dog plasma, the majority of the tretinoin (> 40%) was recovered in the high-density lipoprotein (HDL) fraction. No differences in the plasma distribution between ATRA and **Atragen** were found. These data suggest that a significant percentage of tretinoin associates with plasma lipoproteins (primarily the HDL fraction) upon incubation in human, dog, and rat plasma. Differences between the lipoprotein lipid and protein profiles in human plasma and in dog and rat plasma **influenced** the plasma distribution of ATRA and **Atragen**. Differences in lipoprotein distribution between ATRA and **Atragen** were not observed, suggesting that the drug's distribution in plasma in not **influenced** by its incorporation into these liposomes.

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Concept Details

Tretinoin

An important regulator of gene expression, particularly during growth and development and in neoplasms. Retinoic acid derived from maternal vitamin A is essential for normal gene expression during embryonic development and either a deficiency or an excess can be teratogenic. It is also a topical dermatologic agent which is used in the treatment of psoriasis, acne vulgaris, and several other skin diseases. It has also been approved for use in promyelocytic leukemia.

Related Concepts | View MeSH Information

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- ☐ Main point of item
- ☐ Do not explode this term

With Subheadings: Subheading Definitions

- ☐ administration & dosage
- ☐ adverse effects
- ☐ agonists
- ☐ analogs & derivatives
- ☐ analysis
- ☐ antagonists & inhibitors
- ☐ blood
- ☐ cerebrospinal fluid
- ☐ chemical synthesis
- ☐ chemistry
- ☐ classification
- ☐ contraindications
- ☐ diagnostic use
- ☐ economics
- ☐ history
- ☐ immunology
- ☐ isolation & purification
- ☐ metabolism
- ☐ pharmacokinetics
- ☐ pharmacology
- ☐ physiology
- ☐ poisoning
- ☐ radiation effects
- ☐ standards
- ☐ supply & distribution
- ☐ therapeutic use
- ☐ toxicity
- ☐ urine

MeSH Tree 1

- All MeSH Categories
  - Chemicals and Drugs (MeSH Category)
    - Hormones, Hormone Substitutes, and Hormone Antagonists
      - Hormones
        - Adrenal Cortex Hormones
        - Androgens
        - Estrogens
        - Gastrointestinal Hormones
        - Gonadotropins
        - Hormones, Ectopic
        - Hypothalamic Hormones
        - Invertebrate Hormones
        - Melatonin
        - Natriuretic Hormone
        - Pancreatic Hormones
        - Parotin
        - Peptide Hormones
        - Pituitary Hormones
        - Placental Hormones
        - Pregnancy Proteins
        - Progestational Hormones
        - Sex Hormones
        - Thymus Hormones
        - Thyroid Hormones
        - **Tretinoin**

MeSH Tree 2

- All MeSH Categories
  - Chemicals and Drugs (MeSH Category)
    - Organic Chemicals
      - Hydrocarbons
        - Terpenes
          - Diterpenes
            - Retinoids
              - Vitamin A
              - **Tretinoin**

MeSH Tree 3

- All MeSH Categories
  - Chemicals and Drugs (MeSH Category)
    - Growth Substances, Pigments, and Vitamins
      - Pigments
        - Carotenoids
          - Retinoids
            - Acitretin
            - Etretinate
            - Fenretinide
            - Isotretinoin
            - Retinaldehyde
            - **Tretinoin**
            - Vitamin A